

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/445</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/34612</b> <b>(43) International Publication Date:</b> 13 August 1998 (13.08.98)
<b>(21) International Application Number:</b> PCT/EP98/00648 <b>(22) International Filing Date:</b> 3 February 1998 (03.02.98) <b>(30) Priority Data:</b> 9702392.3 6 February 1997 (06.02.97) GB <b>(71) Applicant (for all designated States except US):</b> THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> PANKHANIA, Mahendra, Govind [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). YURDAKUL, Saruhan [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). <b>(74) Agent:</b> THACKER, Michael, Anthony; The Boots Company plc, Group Patents Dept., D31, 1 Thane Road West, Nottingham NG2 3AA (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS CONTAINING IBUPROFEN AND DOMPERIDONE FOR THE TREATMENT OF MIGRAINE  <b>(57) Abstract</b>  Migraine is treated by administering to the patient a pharmaceutical composition containing a therapeutically effective amount of ibuprofen or a salt thereof and a therapeutically effective amount of domperidone or a salt thereof.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MY	Malaysia	UG	Uganda
CF	Central African Republic	JP	Japan	NE	Niger	US	United States of America
CG	Congo	KE	Kenya	NL	Netherlands	VN	Vietnam
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	YU	Yugoslavia
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand	ZW	Zimbabwe
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LJ	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

## PHARMACEUTICAL COMPOSITIONS CONTAINING IBUPROFEN AND DOMPERIDONE FOR THE TREATMENT OF MIGRAINE

This invention relates to pharmaceutical compositions comprising ibuprofen, and in particular to compositions containing ibuprofen and domperidone useful  
5 for the treatment of migraine.

Ibuprofen, namely 2-(4-isobutylphenyl)propionic acid, is a well known medicament with analgesic, anti-inflammatory and anti-pyretic properties. It is usually sold in the form of racemic ibuprofen (equal amounts of the S(+)-ibuprofen and R(-)-ibuprofen enantiomers). It may also be in the form of  
10 the purified form of either enantiomer, especially S(+)-ibuprofen which is acknowledged to be the active form of racemic ibuprofen. Ibuprofen is also available in salt form, for example the sodium or lysine salt of ibuprofen. Ibuprofen is available under prescription (eg Brufen (RTM)), primarily for the treatment of painful and anti-inflammatory disorders including rheumatoid  
15 arthritis, ankylosing spondylitis, osteoarthritis, postoperative pain, post partum pain and soft tissue injuries, generally at doses up to 3200 mg per day. Ibuprofen is also available as a non-prescription drug (eg Nurofen (RTM)), primarily for the treatment of symptoms of pain and fever including headache, migraine, rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea,  
20 dental pain and colds and flu, generally at doses up to 1200mg per day. The commercially available ibuprofen tablets usually contain 200mg, 400 mg, 600 mg or 800 mg racemic ibuprofen. When an enantiomer or salt of ibuprofen is used the amount of active substance present may be such that the same therapeutic effect is obtained as from the presently-available doses of racemic  
25 ibuprofen. Hereinafter the term "ibuprofen" means any enantiomer of ibuprofen or mixtures of enantiomers including the racemic mixture.

Domperidone, namely 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl-4-piperidiny]-1,3-dihydro-2H-benzimidazol-2-one is a well known medicament with antiemetic properties. Domperidone is available under prescription [eg Motilium (RTM)] as tablets for the treatment of functional dyspepsia at doses of up to 80 mg per day or as tablets, suspensions or suppositories for the treatment of emesis (in nausea or vomiting) at oral doses of up to 120 mg per day. Pharmaceutically acceptable salts, eg the maleate salt of domperidone may be used instead of domperidone itself. In this case the amount of active material is adjusted so as to administer an equivalent amount of base.

Patients suffering from migraine experience advantageous relief of the symptoms of migraine when ibuprofen and domperidone are administered to the patient according to the present invention.

The present invention therefore provides a method of treating migraine which comprises the administration to a patients in need thereof of a pharmaceutical composition comprising a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of domperidone or a pharmaceutically acceptable salt thereof. The amount of ibuprofen in the form of its racemate to be administered is generally in the range 200 to 3200 mg per day in one or more doses throughout the day. Preferably each dose contains 50 to 800 (preferably 50 to 400, more preferably 200 to 400) mg of ibuprofen. The amount of domperidone to be administered is generally in the range 10 to 100 (preferably 20 to 100) mg per day in one or more doses throughout the day. Preferably each dose contains 5

pharmaceutically acceptable salt of either of the active drugs (eg the sodium salt of ibuprofen and/or the maleate salt of domperidone) is used then the amount of drug to be administered should be such that the same therapeutic effect is achieved as from the doses given above. If an enantiomer of ibuprofen

(eg S (+) - ibuprofen) is used, the amount of drug should be such that the same therapeutic effect is achieved as from the doses of racemic ibuprofen given above.

A second aspect of the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of domperidone or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

In the following description of suitable dosage forms containing both active drugs the term "active combination" means a combination of ibuprofen or a pharmaceutically acceptable salt thereof and domperidone or a pharmaceutically acceptable salt thereof. The active combination may comprise the two drugs in intimate admixture but may also comprise combinations in which the two drugs are kept apart for example by coating one or both drugs or physically separating the two drugs for example by using a bilayer tablet in which one drug is present in each layer. The active combination may be prepared by suitable mixing prior to adding to other components of the desired dosage forms or it may be prepared in situ during the production of the desired dosage forms by adding the two drugs separately to the other components of the dosage forms. The amounts of each drug in the active combination in each dosage form should be such that the desired total dose of each drug is taken when the patient takes the pharmaceutical compositions of the present invention as directed. Suitably the pharmaceutical compositions are administered in divided doses throughout the day so the amount of ibuprofen (or the corresponding amount of a salt thereof) to be administered at each dosing time is in the range 50 to 800 mg (preferably 50 to 400, more preferably 200 to 400) mg and the amount of domperidone (or the corresponding amount of a salt thereof) to be administered at each dosing time is 5 to 50 (preferably 5 to 25, more preferably 5 to 20) mg. Therefore, if two

dosage forms are to be administered at each time the dosage forms should contain 25 to 400 (preferably 25 to 200, more preferably 100 to 200) mg ibuprofen and 2.5 to 25 (preferably 2.5 to 12.5, more preferably 2.5 to 10) mg of domperidone (or the corresponding amounts of their salts).

5       The pharmaceutical compositions of the present invention may be administered orally, rectally, parenterally, buccally or topically, preferably orally. Suitably the pharmaceutical compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral, buccal or topical administration. Pharmaceutically acceptable  
10       diluent or carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 1-99% by weight of active combination.

      Solid compositions for oral administration are preferred compositions of the invention. Solid compositions of the invention are preferably prepared in unit  
15       dosage form and are the known pharmaceutical forms for such administration, for example tablets and capsules. Suitably tablets may be prepared by mixing the active combination with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known  
20       methods. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active combination optionally in the form of beads with or without added excipients, may be prepared by conventional means and, if desired, provided

      manner known to those skilled in the art so as to give a controlled release of the compound of the present invention. Other compositions for oral administration include oily suspensions containing a compound of the present invention in a

suitable vegetable oil, for example arachis oil or aqueous solutions or suspensions.

Preferably, a solid composition comprises a) 10-99% active combination; b) 1-90% of a diluent and c) 0.1-10% of a lubricating agent, d) 0.1-15% of a disintegrating agent and optionally e) 0.1-15% of a binder. Optionally 0.1-10% of a flow aid may be added.

Suitable diluents include lactose, calcium phosphate, dextrin, microcrystalline cellulose, sucrose, starch, modified starch, calcium sulphate or mixtures thereof. Suitable lubricating agents include magnesium stearate, stearic acid, calcium stearate, sodium stearyl fumarate (sold under the trade name PRUV), hydrogenated vegetable oils or mixtures thereof. Preferably the lubricating agent is magnesium stearate or stearic acid. Suitable disintegrating agents include maize starch, sodium starch glycollate, low substituted hydroxypropyl cellulose, alginic acid, calcium carboxymethyl cellulose, croscarmellose sodium or mixtures thereof. Suitable binders includes polyvinyl pyrrolidone, gelatin, hydroxypropylmethyl cellulose, starch or mixtures thereof. Preferably the binder is polyvinylpyrrolidone. Suitable flow aids include talc and colloidal silicon dioxide. It will be appreciated by those skilled in the art that a particular excipient may perform more than one function for example maize starch may act as a diluent, a binder or as a disintegrating agent.

Controlled release forms of the pharmaceutical compositions of the present invention include rapid release formulations such as soluble granules or melt filled fast release capsules, delayed release formulations such as tablets provided with enteric coatings, for example, of cellulose acetate phthalate and, in particular, sustained release formulations. Numerous types of sustained release formulations are known to those skilled in the art. Typically, the active combination may be encapsulated within a release retarding coating, for example, a copolymer of cellulose ether and acrylate, or may be bound to small

particles such as, for example, ion exchange resin beads. Alternatively, the active combination may be incorporated into a matrix containing a release retarding agent such as a hydrophilic gum e.g. xanthan gum, a cellulose derivative e.g. hydroxypropyl methylcellulose, or a polysaccharide, wax or plastics material. Such techniques may provide sustained blood levels of ibuprofen and domperidone by controlling, for example, erosion, swelling, disintegration and dissolution of the composition within the gastrointestinal tract.

The active combination may be formulated into a solid dosage form in which the two active drugs are kept separate. For example, the dosage form may be a bilayer tablet in which the active drugs are contained in different layers. The different layers can be formulated so as to provide the optimum release profile for each drug.

Liquid fill compositions for example viscous liquid fills, liquid paste fills or thixotropic liquid fills are also suitable for oral administration. Melt filled compositions may be obtained by mixing the active combination with certain esters of natural vegetable oil fatty acids, for example, the Gelucire (Trademark) range available from Gattefosse to provide a variety of release rates. Suitably a melt-filled capsule comprises a) 10-80% active combination and b) 20-90% of a fatty acid ester excipient which comprises one or more polyol esters and triglycerides of natural vegetable oil fatty acids.

Solid compositions designed to effervesce when added to water to form an effervescent solution or suspension are also suitable for oral administration. Suitably an effervescent composition comprises a) 1-50% of active combination

may be presented in the form of tablets or granules. Preferably, effervescent compositions additionally comprise a taste masking component for example a sweetener, a flavouring agent, arginine, sodium carbonate or sodium bicarbonate.



Solid non-effervescent compositions are preferred compositions of the present invention.

Preferably oral liquid compositions comprise a) 0.1-10% active combination possibly as coated particles b) 1-50% of a diluent c) water to 100%. Optionally  
5 the composition may contain suspending agents, thickeners, cosolvents such as alcohol and/or preservatives. Suitable diluents include sweetening agents for example sorbitol, xylitol, sucrose, or LYCASIN® (registered trademark of Roquette). Suitable suspending agents or thickeners include cellulose gums, agar or natural gums, for example xanthan gum. Flavourings or other  
10 taste-masking agents known to those skilled in the art for example saccharin, sodium saccharin, acesulpham K or aspartame may be added.

Compositions for topical administration may be prepared by dispersing the active combination in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active combination in a  
15 topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. A suitable cream comprises a) 1-15% active combination; b) 5-40% of an oily phase; c) 5-15% of an emulsifier; d) 30-85% of water. Suitable oily phases comprise petrolatum and/or light liquid paraffin. Alternatively, the active combination may be distributed in a base  
20 comprising a) 10-40% of a self emulsifying base; b) 60-90% of water to form a cream. LABRAFILL and GELOT (both tradenames of Gattefosse) are examples of self emulsifying bases. An ointment may be prepared by mixing the active combination with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A suitable ointment comprises a)  
25 1-15% active combination and b) a topical vehicle to 100%. A gel may be prepared by mixing the active combination with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water. Suitable gels comprise a) 1-15% active combination; b) 1-20% of a gelling agent; c)

0.01-10% of a preservative and d) water to 100%. Preferably the gelling agent comprises 0.1-10% of a carbomer and a neutralising agent.

Suitable topically administrable compositions may also comprise a matrix in which the active combination is dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally, for example in a patch or poultice. A suitable transdermal composition may be prepared by mixing the active combination with a topical vehicle, such as described above, together with a potential transdermal accelerant such as dimethyl sulphoxide, propylene glycol or peppermint oil.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with polyethylene glycol bases or semi-synthetic glycerides. Preferably the composition in the form of a suppository comprises 10-30% active combination and 70-90% of a carrier wherein the carrier is selected from a base which comprises polyethylene glycol or a semi-synthetic glyceride.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions of the active combination in a suitable solvent.

Spray formulations may be prepared by dissolving or suspending the active combination in a liquid medium which may also contain other ingredients such as stabilising agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. For example, a spray may be prepared by dissolving

co-solvent (eg alcohol). The two phases are then mixed and the resulting mixture filtered and placed into dispensing containers. The dispensing containers may be fitted with a metered, manually-operated spray mechanism or the dispenser may contain a pressurised propellant and be fitted with a

suitable dispensing valve. The spray and dispensing container may be adapted for nasal administration of the spray

In some formulations it may be beneficial to use the active combination in the form of particles of very small size, for example as obtained by fluid energy  
5 milling.

In the compositions of the present invention the components of the active combination may, if desired, be associated with other compatible pharmacologically active ingredients and/or enhancing agents.

The invention will now be illustrated by the following Examples which are  
10 given by way of example only.

In these examples the ingredients are obtained from the sources listed below:-

Microcrystalline cellulose is available from FMC Corporation under the trade name Avicel P.H. 101;

15 Polyvinylpyrrolidone is available from GAF (GB) Limited under the trade name Plasdone K29-32;

Croscarmellose sodium is available from FMC Corporation under the trade name Ac-Di-Sol;

Colloidal silicon dioxide is available from Degussa under the trade name  
20 Aerosil 200; and

Calcium carboxymethyl cellulose is available from Carnation Gums, London under the trade name ECG 505.

Example 1

The example composition comprises the following ingredients:-

		<u>% w/w</u>
5	Ibuprofen	57
	Domperidone	2.85
	Tricalcium phosphate	20.15
	Microcrystalline cellulose	6
	Polyvinylpyrrolidone (Plasdone)	3
10	Croscarmellose sodium	10
	Stearic acid	1

The composition is prepared according to the following stages:-

- a) the ibuprofen, domperidone, tricalcium phosphate, croscarmellose sodium and microcrystalline cellulose are sieved and blended to form a  
15 homogeneous mixture;
- b) the mixture is granulated with polyvinylpyrrolidone and then dried;
- c) the dried granules are blended with stearic acid;
- d) the lubricated granule is compressed to form tablet cores each containing  
20 ibuprofen and 20mg of domperidone; and

e) the tablet cores are coated with a film coating comprising the following ingredients:-

	<u>% w/w</u>
Hydroxypropylmethyl cellulose	65
Titanium dioxide	20
French chalk	15

### 5 Example 2

In the same manner as described in Example 1 is prepared the composition of Example 2 comprising the following ingredients in the form of tablets each containing 200 mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10 mg of domperidone.

10		<u>% w/w</u>
	Ibuprofen	60
	Domperidone	1.5
	Tricalcium phosphate	18.5
	Microcrystalline cellulose	5.9
15	Polyvinylpyrrolidone (Plasdone)	3.9
	Croscarmellose sodium	9.6
	Stearic acid	0.6

### Example 3

The example composition comprises the following ingredients:

	<u>% w/w</u>
Ibuprofen	60.4
Domperidone base (in the form of its maleate salt)	1.51
Tricalcium phosphate	18.2
5 Microcrystalline cellulose	6
Polyvinylpyrrolidone (Plasdone)	3.6
Croscarmellose sodium	9.7
Magnesium stearate	0.6

The composition is prepared according to the following stages:-

- 10 (a) the domperidone maleate and microcrystalline cellulose were triturated;
- (b) the ibuprofen, tricalcium phosphate, croscarmellose sodium and triturated mixture from (a) are sieved and blended to form a homogeneous mixture;
- 15 (c) the mixture is granulated with a solution of polyvinylpyrrolidone in propan-2-ol and then dried;
- (d) the dried granules are blended with magnesium stearate;

20 containing 200 mg of ibuprofen and 5 mg of domperidone base in the form of its maleate salt or each containing 400 mg of ibuprofen and 10 mg of domperidone in the form of its maleate salt ; and

- (e) the tablet cores are coated with a film coating comprising the following ingredients:-

	<u>% w/w</u>
Hydroxypropylmethylcellulose	65
5 Titanium dioxide	20
French chalk	15

#### Example 4

In a similar manner to that described in Example 3, compositions containing 200 mg of ibuprofen and 2.5 mg of domperidone base (in the form of its maleate salt) or 400 mg of ibuprofen and 5 mg of domperidone base (in the form of its maleate salt) are prepared from the following ingredients:-

	<u>% w/w</u>
Ibuprofen	60.8
Domperidone base (in the form of its maleate salt)	0.76
15 Microcrystalline cellulose	6.1
Tricalcium phosphate	18.2
Croscarmellose sodium	9.7
Polyvinylpyrrolidone	3.6
Magnesium stearate	0.6

Example 5

In a similar manner to that described in Example 3, compositions containing 200 mg of ibuprofen and 10 mg of domperidone base (in the form of its maleate salt) or 400 mg of ibuprofen and 20 mg of domperidone base (in the form of its maleate salt) are prepared from the following ingredients:-

	<u>% w/w</u>
Ibuprofen	59.5
Domperidone base (in the form of its maleate salt)	2.97
Microcrystalline cellulose	5.95
10 Tricalcium phosphate	17.9
Croscarmellose sodium	9.5
Polyvinylpyrrolidone	3.6
Magnesium stearate	0.6

Example 6

15 The composition of Example 6 comprises the following ingredients:-

	<u>% w/w</u>
Ibuprofen	56
Domperidone	2.8
Maize starch	37.2
	5.2
Stearic acid	0.3

The composition is prepared according to the following steps:-



- (a) the ibuprofen, domperidone and maize starch are sieved and blended to form a homogeneous mixture;
- (b) the mixture is granulated with water and allowed to dry;
- (c) the dried granules are blended with dried maize starch and stearic acid;
- 5 (d) the lubricated granule is compressed to form tablet cores each containing 200 mg of ibuprofen and 10 mg of domperidone or each containing 400 mg of ibuprofen and 20 mg of domperidone;
- (e) the tablet cores are coated with a sugar coating comprising the following ingredients:-

		<u>% w/w</u>
	Opaglos regular	1.0
	Acacia gum	1.0
	Refined sugar	73.5
5	Calcium sulphate	23.5
	Sodium carboxymethyl cellulose	1.0

Example 7

In the same manner as described in Example 3 the composition of Example 7 is prepared comprising the following ingredients in the form of tablets each containing 200 mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10 mg of domperidone:-

		<u>% w/w</u>
	Ibuprofen	59
	Domperidone	2
15	Maize starch	35
	Dried maize starch	3.5
	Stearic acid	0.5

Example 8

	<u>% w/w</u>
Ibuprofen	70
Domperidone	3.5
Sodium lauryl sulphate	0.3
5 Maize starch	19.3
Pregelised starch	5.6
Colloidal silicon dioxide	0.4
Magnesium stearate	0.9

The example composition is prepared according to the following stages:-

- 10 a) the ibuprofen, domperidone, sodium lauryl sulphate, maize starch, pregelised starch, silicone dioxide and magnesium stearate are blended together to form a homogeneous mixture; and
- b) the mixture is filled into hard gelatin capsules, each containing 200 mg of ibuprofen and 10mg of domperidone or each containing 400 mg of
- 15 ibuprofen and 20 mg of domperidone.

#### Example 9

In the same manner as described in Example 8, the composition of Example 9 is prepared comprising the following ingredients to give capsules each containing 200mg of ibuprofen and 5 mg domperidone or each containing

20 400 mg of ibuprofen and 10 mg of domperidone.

		<u>% w/w</u>
	Ibuprofen	75.5
	Domperidone	1.89
	Sodium lauryl sulphate	0.3
5	Maize starch	15.41
	Pregelised starch	6
	Colloidal silicon dioxide	0.4
	Magnesium stearate	0.5

Example 10

- 10 The composition of Example 10 is prepared comprising the following ingredients:-

		<u>% w/w</u>
	Ibuprofen	61.54
	Domperidone	3.08
15	Microcrystalline cellulose	10.22
	Croscarmellose sodium	14.62
	Stearic acid	0.54
	Pregelised starch	10.00

The example composition is prepared as follows:

and the pregelised starch are granulated with water.

- 2) The granules are dried and sized, blended with the other ingredients and compressed into tablets which are then film coated.

### Example 11

In a similar manner to that described in Example 10, the composition of Example 11 is prepared from the following ingredients to give tablets each containing 200 mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10 mg of domperidone.

	<u>% w/w</u>
Ibuprofen	61.54
Domperidone	1.54
Microcrystalline cellulose	10.89
Croscarmellose sodium	15.49
Stearic acid	0.54
Pregelised starch	10.00

### Example 12

The composition of Example 12 is prepared from the following ingredients to give tablets each containing 200 mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10mg of domperidone.

	<u>% w/w</u>
Ibuprofen	57.14
Domperidone	1.43
Microcrystalline cellulose	29.72
5 Polyvinylpyrrolidone	0.71
Stearic acid	0.50
Colloidal silicon dioxide	0.50
Calcium carboxymethyl cellulose	10.00

The composition is prepared in the following manner

- 10 1) The ibuprofen, microcrystalline cellulose, part (21%) of the calcium carboxymethyl cellulose and part (50%) of the colloidal silicon dioxide are granulated using a solution of polyvinylpyrrolidone in propan-2-ol.
- 2) The granules are sized and dried to remove propan-2-ol.
- 15 3) The dried granules are blended with the remaining ingredients and compressed into tablets which may be coated if required.

### Example 13

In a similar manner to that described in Example 12 the following

20 10 mg of domperidone.

	<u>% w/w</u>
Ibuprofen	57.14
Domperidone	2.86
Microcrystalline cellulose	28.29
5 Polyvinylpyrrolidone	0.71
Stearic acid	0.50
Colloidal silicon dioxide	0.50
Calcium carboxymethyl cellulose	10.00

#### Example 14

- 10 A bilayer tablet which contains 200 mg of ibuprofen in a sustained release layer and 10 mg of domperidone in the other layer from which it is released soon after ingestion is prepared from the following ingredients.

	<u>% w/w</u>
Ibuprofen containing layer	
15 Ibuprofen	77.22
Polyvinylpyrrolidone	2.51
Stearic acid	1.00
Xanthan gum	19
Colloidal silicon dioxide	0.27
20 Domperidone containing layer	
Domperidone	4.12
Tricalcium phosphate	56.78
Microcrystalline cellulose	18.52
Polyvinylpyrrolidone	4.12
25 Croscarmellose sodium	15.64
Magnesium stearate	0.82

The method of making the tablet is as follows:

A) Ibuprofen-containing layer

The ibuprofen, 3% of the xanthan gum are mixed and granulated using polyvinylpyrrolidone in propan-2-ol. The granules are dried, sized and then  
5 blended with the remaining ingredients.

B) Domperidone-containing layer


The domperidone, tricalcium phosphate, microcrystalline cellulose and croscarmellose sodium are mixed and granulated using polyvinyl-  
pyrrolidone in aqueous propan-2-ol. The granules dried, sized and blended  
10 with the remaining ingredients.

C) Tablet production

Using a bilayer tableting press, the domperidone-containing layer is compressed followed by the ibuprofen-containing layer to give bilayer tablets which may be coated if required

15 Example 15

The composition of Example 15 is prepared by mixing the ingredients listed below and preparing tablets each containing 200mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10 mg of domperidone by direct compression.





	Ibuprofen	78.03
	Domperidone	1.95
	Microcrystalline cellulose	10.92
	Stearic acid	1.95
5	Lactose	5.19
	Sodium lauryl sulphate	1.05
	Colloidal silicon dioxide	0.12
	Magnesium stearate	0.78

Example 16

- 10 In a similar manner to that described in Example 16, directly compressed tablets each containing 200 mg of ibuprofen and 10 mg of domperidone are prepared from the following ingredients:-

		<u>% w/w</u>
	Ibuprofen	78.93
15	Domperidone	3.90
	Microcrystalline cellulose	8.97
	Stearic acid	1.95
	Lactose	5.19
	Sodium lauryl sulphate	1.05
20	Colloidal silicon dioxide	0.12
	Magnesium stearate	0.78

Pharmaceutical compositions of the present invention may also be prepared by replacing the ibuprofen in any one of Examples 1 to 16 by the equivalent amount of an ibuprofen salt (eg the sodium salt) or the  
25 activeS(+)-enantiomer thereof and/or by replacing the domperidone by the equivalent amount of a salt of domperidone (eg the maleate salt).

Claims

1. A method of treating migraine which comprises the administration to a patient in need thereof of a pharmaceutical composition comprising a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of domperidone or a pharmaceutically acceptable salt thereof.
2. A method as claimed in claim 1 wherein 200-3200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 10-100 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt are administered per day.
3. A method as claimed in claim 1 wherein 200-3200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 20-100 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt are administered per day.
4. A method as claimed in any preceding claim wherein more than one dose is given during the day, each dose comprising 50 to 800 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 5 -50 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.
5. A method as claimed in any preceding claim wherein more than one dose corresponding amount of a pharmaceutically acceptable salt or enantiomer and 5 -25 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

6. A method as claimed in any preceding claim wherein more than one dose is given during the day, each dose comprising 200 to 400 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 5 -20 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

7. A pharmaceutical composition comprising for the treatment of migraine a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of domperidone or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition as claimed in claim 7 comprising 25 to 400 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5 to 25 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

9. A pharmaceutical composition as claimed in claim 7 or claim 8 comprising 25 to 200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5 to 12.5 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

10. A pharmaceutical composition as claimed in any one of claims 7 to 9 comprising 100 to 200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5-10 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

11. The use of a combination of a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of domperidone or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of migraine.

12. The use in the preparation of a medicament as claimed in claim 11 in which each unit dose of the medicament comprises 25 to 400 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5 to 25 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

13. The use in the preparation of a medicament as claimed in claim 11 or claim 12 in which each unit dose of the medicament comprises 25 to 200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5 to 12.5 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

14. The use in the preparation of a medicament as claimed in any one of claims 11 to 13 in which each unit dose of the medicament comprises 100 to 200 mg of ibuprofen or the corresponding amount of a pharmaceutically acceptable salt or enantiomer and 2.5-10 mg of domperidone or the corresponding amount of a pharmaceutically acceptable salt.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/00648

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/445

According to International Patent Classification(IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 020 018 A (DON L. SIMMONS) 28 December 1991	1,7,11
Y	see claims 1-3,7,8	2-6, 8-10, 12-14
P,X	GB 2 313 309 A (NINH ON) 26 November 1997 see abstract	1,7,11
Y	Z.ZAHUMENSZKY ET AL.: "The role of a peripheral dopamine-antagonist (Motilium) in improving the tolerance to steroidal and non-steroidal anti-inflammatory agents" THERAPIA HUNGARICA, vol. 38, no. 4, 1990, pages 156-159, XP002068869 see page 158; table IV	1-14
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

22 June 1998

Date of mailing of the international search report

06/07/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Tzschoppe, D

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/00648

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT.

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>D.KLINGLER ET AL.: "Migräne-Therapie"  OESTERREICHISCHE AERZTEZEITUNG,  vol. 49, no. 24, 1994,  pages 26-30, XP002068870  see page 27</p> <p>-----</p>	1-14

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/EP 98/00648

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CA 2020018	A	28-12-1991	US 5273759 A	28-12-1993
GB 2313309	A	26-11-1997	NONE	

THIS PAGE BLANK (USPTO)